To begin, Claims 11 and 12 are rejected under 35 U.S.C. §103(a) as being obvious over Göschel, et al., (Experimental Neurology 1997, 147:96-102) in view of Borodic, et al., (Ophthalmic Plastic and Reconstructive Surgery, 9:182-190). The Office concludes that Göschel, et al. disclose that neutralizing antibodies were found in the sera of all non-responders (pages 98-99) and that the presence of neutralizing antibodies is the cause of therapeutic failure (page 101). The Office contends that Borodic, et al. teach the use of botulinum neurotoxin type B for adjuvant therapy for subjects who are resistant or refractory to botulinum A toxin. The Office concludes that it would be *prima facie* obvious to combine the teaching of Göschel, et al. with the teaching of Borodic, et al. to arrive at the instant invention.

The instant method is drawn to the administration of a botulinum neurotoxin from *Clostridium botulinum* wherein the neurotoxin is free of the complexing proteins which naturally form complexes with botulinum neurotoxins. The Applicants acknowledge that Göschel, et al. disclose administration of botulinum neurotoxin for several therapeutic indications. The Applicants also acknowledge that Göschel, et al. do not disclose a botulinum neurotoxin or a mixture of two or more botulinum neurotoxins which are free of complexing proteins which naturally form complexes with botulinum neurotoxins, as noted by the Office. The Applicants further note that the cited prior art also do not disclose this claim limitation. Therefore, the Office basis for rejection under obviousness is improper because the prior art do not teach or suggest a botulinum neurotoxin free of the complexing proteins which naturally form complexes with botulinum neurotoxins for the treatment of patients already exhibiting neutralizing antibodies to a known botulinum serotype. The Applicants respectfully request reconsideration of the rejections in view of this response.

Similarly, the Office rejects Claims 11-13 under 35 U.S.C. 103(a) for obviousness over Göschel, et al. in view of Shelley, et al., (J Am Acad Dermatol. 1998, 28:227-9) in view of Borodic, et al. The Office concludes that Göschel, et al. teach a method of treating patients having the claimed therapeutic indications treatable with botulinum neurotoxin A. The Office views Shelley, et al. to teach a method of treating patients with hyperhidrosis using botulinum toxin A therapy. The Office cites

Borodic, et al. as teaching the use of botulinum toxin B as an alternative to botulinum toxin A in patients who have developed neutralizing antibodies.

The Applicants acknowledge that Göschel, et al. and Shelley, et al. disclose conditions for which botulinum therapy is indicated. The Applicants acknowledge that Borodic, et al. disclose botulinum toxin B complex as a replacement for botulinum A toxin complex in patients who have developed neutralizing antibodies. However, as discussed previously, the cited references do not disclose administration of a botulinum neurotoxin which is free of the complexing proteins which naturally form complexes with botulinum neurotoxins. Reconsideration and withdrawal of the prior art rejection is respectfully solicited.

Moving on, the Office rejects Claims 11-12 and 14-15 under 35 U.S.C. 103(a) as being obvious over Keen, et al. (Plastic and Reconstructive Surgery, July 1994, 94, No. 1, pages 94-99) and further in view of U.S. Patent No. 5,512,547, published April 30, 1996.

The Office concludes that Göschel, et al. teach a method of treating patients having the claimed therapeutic indications which are treatable with botulinum neurotoxin A. The Office finds Keen, et al. to teach a method of treating patients with hyperkinetic facial lines using botulinum toxin A therapy. Borodic, et al. teach botulinum toxin B as an alternative to botulinum toxin A. The Office concludes it would be *prima facie* obvious to treat patients having the disorders disclosed in Göschel, et al. and Keen, et al. and who have developed neutralizing antibodies, with botulinum toxin B, as suggested by Borodic, et al. No basis is given for rejection based on the disclosure of U.S. Patent No. 5,512,547, which patent discloses a shelf stable botulinum toxin preparation which is stable on lyophilization, but which neurotoxin preparation is not disclosed to be free of the complexing proteins associated with neurotoxin complexes.

The Applicants submit that the combination of Göschel, et al., Keen, et al. and Borodic, et al. fails for the same reasons noted above, namely the cited prior art do not suggest, nor make obvious a *Clostridium botulinum* neurotoxin, which is free of

complexing proteins which naturally form complexes with botulinum neurotoxins for the treatment of subjects already exhibiting neutralizing antibodies to neurotoxin complexes. The Applicants respectfully request reconsideration and withdrawal of the rejection.

The Office rejects Claims 11-12 under 35 U.S.C. § 103(a) as being obvious over Göschel, et al. in view of Borodic, et al. and further in view of Jankovic, et al., (The New England Journal of Medicine, April 25, 1991). The Office opines that it would be *prima facie* obvious to treat patients having the claimed indications for botulinum toxin therapy as disclosed in Göschel, et al. with botulinum toxin B as an alternative to botulinum toxin A as disclosed Borodic, et al. or with other known toxin types as disclosed in Jankovic, et al.

The proposed combination fails because the instant invention is distinguished from Göschel, et al. and Borodic, et al. as per the previous discussion. Moreover, the combination fails because Jankovic, et al. teach substitution with botulinum toxin of known serotypes, not a botulinum neurotoxin which is free of complexing proteins. Reconsideration and withdrawal of the prior art rejection is respectfully requested.

The Applicants submit that the non-obviousness of the instant invention resides in novel performance characteristics of the instant botulinum neurotoxin, which is free of the complexing proteins which naturally form complexes with botulinum neurotoxins, and the discovery that patients exhibiting neutralizing antibodies can be effectively treated with such a botulinum neurotoxin. No cited reference discloses such preparation or makes such preparation obvious. In light of these remarks, we submit the Office has not established a *prima facie* basis for rejecting the claims for obviousness.

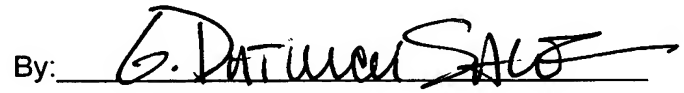
* * * * *

Accordingly, reconsideration of all grounds of objection and rejection, withdrawal thereof, and passage of this application to issue are all hereby respectfully solicited.

It should be apparent that the undersigned attorney has made an earnest effort to place this application into condition for immediate allowance. If he can be of assistance to the Examiner in the elimination of any possibly-outstanding insignificant impediment to an immediate allowance, the Examiner is respectfully invited to call him at his below-listed number for such purpose.

Allowance is solicited.

Respectfully submitted,
THE FIRM OF HUESCHEN AND SAGE

By: 
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